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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 07/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,581	HANNA ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-36* is/are pending in the application.

4a) Of the above claim(s) *28,30,31,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-27,29,32 and 33* is/are rejected.

7)☒ Claim(s) *34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The Election filed September 23, 2002 (Paper No. 6) in response to the Office Action of August 21, 2002 is acknowledged and has been entered. Additionally, the response filed January 27, 2003 is acknowledged and has been entered.

Claims 23-36 are pending.

Claims 28, 30-31, and 35-36 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 23-27, 29, and 32-34 are currently under prosecution.

The elected species of "cervical cancer" (Claim 29) is found to be free of the art. Thus, the next species of "breast cancer" will be examined with cervical cancer.

Applicant's election with traverse of Group I, claims 23-27, 29, and 32-34 in Paper No 6 is acknowledged. It is further noted that applicant's have elected the species of "cervical cancer" in Claim 29 and "papillomavirus E7 antigen" in Claim 33. The traversal is on the ground(s) that the inventions are generic in nature and that other neoplastic disease will also be treatable using adjuvants according to the invention. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 5. Furthermore, the species identified represent distinct cell types with different morphologies and functions which would require different searches and the consideration of different patentability issues.

Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

Claim 27 is objected to for reciting "parasitic infection and viral infection" which are drawn to non-elected groups. Applicant is requested to amend the claims solely to treatments directed at neoplasms or cancer.

Claim 34 is objected to as being dependent from a previously cancelled claim, i.e. Claim 34 refers back to Claim 1 which was cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite because is not clear what the improved method is aimed at treating.

Claim 24 recites the limitation "secreted" in Claim 23. There is insufficient antecedent basis for this limitation in the claim.

Claim 26 recites the limitation "TGF antagonist" in Claim 25. There is insufficient antecedent basis for this limitation in the claim. This rejection can be obviated by amending Claim 26 to recite TGFβ antagonist.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25-26, 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: in a method of treatment for neoplasms or cancer which includes the induction of a cytotoxic T-lymphocyte response wherein the improvement comprises (i) the administration of an adjuvant which induces a cytotoxic T-lymphocyte response and (ii) the administration of antagonist of an immunosuppressive factor wherein said factor is TGFβ; wherein the administration of adjuvant and antagonist is effected sequentially or concurrently, and in any order, does not reasonably provide enablement for the method as broadly claimed. Further, while being enabling for: a method of treating neoplastic or cancerous growth comprising administering to a patient in need thereof: (a) an admixture comprising a cancer or tumor antigen expressed by said cancer cells and a microfluidized antigen formulation, said antigen formulation comprising: a stabilizing detergent, a micelle-forming agent, and a biodegradable and biocompatible oil, said antigen formulation being formulated as a stable oil-in-water emulsion; wherein said admixture is administered to said patient in an amount sufficient to induce a CTL response in said patient which is specific for the cancer or tumor antigen contained in said admixture, and (b) a therapeutically effective amount of at least one agent

which is capable of neutralizing or down regulating the activity of TGFβ - does not reasonably provide enablement for the method as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an improved method of treatment comprising administering an adjuvant which induces a CTL response and an antagonist of an immunosuppressive factor; wherein the administration of adjuvant and antagonist is effected sequentially or concurrently, and in any order. The claims are further drawn to a method of treating cancer comprising administering a cancer or tumor antigen expressed by said cancer cells and a therapeutically effective amount of at least one agent which is capable of neutralizing or down regulating the activity of tumor and host-secreted immunosuppressive factors.

This includes administering any and all adjuvants which induce a CTL response or tumor-associated antigens and any and all antagonists to any known or unknown immunosuppressive factor.

The specification teaches (page 6, last paragraph) examples of soluble inhibitory or immunosuppressive factors or cytokines which are secreted by tumor cells in order to avoid

immune destruction such as TGFβ, interleukin 10, prostaglandin (PGE2), immunosuppressive acidic protein (IAP), and lipocortin-1 (LC1). However, with regards to antagonists of such immunosuprresive factors, the specification only provides examples of antagonists of TGFβ (i.e. anti-TGFβ antibodies) in combination with an adjuvant which induces a CTL response (pages 16-17).

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to methods of treatment wherein said treatment is undefined (or wherein said method comprises treating cancer) comprising employing any and all antagonists to any known or unknown immunosuppressive factor, and applicant has not enabled all of these types of antagonists because it has not been shown that these antagonists are capable of functioning as that which is being disclosed. In the absence of specific antagonists to TGFβ, there is insufficient guidance and or objective evidence of what other antagonists are included, what they target, or how cellular physiology is affected by their administration in vitro or in vivo. Further, there is no assessment of their potential toxicity, immunogenicity, metabolism, or predictability in treating cancer in vivo. All of this underscores the criticality of providing workable examples which are not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure that any and all such antagonists to any and all potential immunosuppressive factors will effect any and all treatment modalities as predicted.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23-25, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Wojtowicz-Praga *et al.* (Jnl. Immunology. May 1996, Vol. 19. No. 3, pages 169-175).

Wojtowicz-Praga *et al.* teach a method of treating cancer comprising administering an antagonist of TGFβ and an adjuvant which induces a cytotoxic T-lymphocyte response wherein the administration of adjuvant and antagonist are administered sequentially. Specifically, the reference teaches the administration of anti-TGFβ antibody intraperitoneally (i.p.) into mice every other day and i.p. injections of interleukin-2 twice daily (page 171, 1st column, 2nd paragraph). The reference further teaches (page 170, 2nd column) that IL-2 stimulates the immune system including the growth of T cells and LAK cells, and also augments the cytolytic activity of natural killer (NK) cells, and augments the cytotoxicity of monocytes- all of which read on an adjuvant (IL-2) which induces a cytotoxic T-lymphocyte response.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23-27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wojtowicz-Praga *et al.* (Jnl. Immunology. May 1996, Vol. 19. No. 3, pages 169-175) in combination with the teachings of Arteaga *et al.* (J.Clin.Invest., December 1993, Vol. 92, pages 2569-2576) in further view of Segarini *et al.* (WO 94/09815, 1994, IDS).

1. Wojtowicz-Praga *et al.* teach as set forth above w/ regards to Claims 23-25, and 27.
2. Wojtowicz-Praga *et al.* to not specifically teach administering the adjuvant intradermally, intramuscularly or subcutaneously and administering the TGF antagonist intravenously (Claim 26). Further, Wojtowicz-Praga *et al.* do not specifically teach wherein said cancer is comprises breast cancer (Claim 29).

3. Arteaga *et al.* teach a method of treating breast cancer in-vivo by administering anti-TGFβ antibodies (Figure 3, page 2571; Table I, page 2572; Figure 5, page 2572).
4. Segarini *et al.* teach methods of treating diseases associated with excess TGFβ, including cancer, by administering soluble receptor fragments resembling the extracellular portion of TGFβ which can be administered subcutaneously, intravenously, intradermally or intraperitoneally (top of page 21).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the method of Wojtowicz-Praga *et al.* so as to include the treatment of breast cancer because both references successfully teach methods of treating cancerous conditions comprising administering anti-TGFβ antibodies. Further, one would have been motivated to include the treatment of breast cancer cells because Wojtowicz-Praga *et al.* teach that there is a positive association between TGFβ and states of enhanced tumorigenesis wherein high levels of TGFβ activity were reported in media conditioned by hormone-independent, highly tumorigenic breast cancer cells and TGFβ-1 mRNA transcripts were more abundant in highly proliferative tumor than in non-tumor human mammary tissues (bottom of page 169- to top of page 170). Hence, based on the successful teachings of Arteaga *et al.*, using neutralizing anti-TGFβ antibodies, one of ordinary skill in the art would have a reasonable expectation of success that the methods of Wojtowicz-Praga *et al.*, who also employed neutralizing anti-TGFβ antibodies in combination with IL-2 would also treat breast cancer. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to vary the routes of administration including

administering the IL-2 adjuvant intradermally, intramuscularly or subcutaneously and administering the anti-TGFβ antibodies intravenously because Segarini *et al.* (WO 94/09815, 1994, IDS) teach methods of treating diseases associated with excess TGFβ, including cancer, by administering soluble receptor fragments resembling the extracellular portion of TGFβ which can be administered subcutaneously, intravenously, intradermally or intraperitoneally (top of page 21). Further, it is well within the level of ordinary skill in the art to determine optimum parameters of administration.

Claims 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Raychaudhuri *et al.* (US Patent No. 5,695,770, June 1995, IDS) in combination with the teachings of Hoefer *et al.* (Cancer Immunol. Immunother, 1995, Vol. 41, pages 302-308) or Arteaga *et al.* (J.Clin.Invest., December 1993, Vol. 92, pages 2569-2576).

1. Raychaudhuri *et al.* teach methods of treating neoplastic or cancerous growths (column 6, line 26) comprising administering to a patient an admixture comprising a cancer or tumor antigen expressed by said cancer in an amount sufficient to induce a cytotoxic T-lymphocyte response (abstract) wherein said antigen formulation comprises and a microfluidized antigen formulation comprising a stabilizing detergent, a micelle-forming agent, and a biodegradable and biocompatible oil wherein said antigen formulation is formulated as a stable oil-in-water emulsion (column 4, lines 29+) Raychaudhuri *et al.* further teach that said antigen is selected from the group consisting of papillomavirus E7 protein (column 6, lines 4-5; column 20, lines 45+).

2. Raychaudhuri *et al.* do not teach the antigen formulation above *in combination* with a therapeutically effective amount of at least one agent which is capable of neutralizing or down regulating the activity of tumor and host-secreted immunosuppressive factors.
3. Hoefer *et al.* teach a method of treating cancer comprising an agent which is capable of neutralizing or down regulating the activity of TGFβ wherein said agent is an anti-TGFβ antibody and/or TGFβ antagonist. Hoefer *et al.* further teach that said composition is useful for treating cancer (abstract; and page 305, 2nd column). Hoefer *et al.* further teach that treatment with the TGFβ antagonist showed a dramatic suppression of the development of primary tumors, and that all treated mice showed a complete or at least partial suppression of the development of distant metastases (page 306, 1st column).
4. Arteaga *et al.* also teach methods of treating cancer in-vivo by administering anti-TGFβ antibodies (Figure 3, page 2571; Table I, page 2572; Figure 5, page 2572).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the antigen formulation of Raychaudhuri *et al.* with the TGFβ antagonist of Hoefer *et al.* and/or alternatively, the anti-TGFβ antibodies of Arteaga *et al.* since all three agents have individually been taught in the prior art to be useful for the treatment of cancer. One would have been motivated to do so because Raychaudhuri *et al.* successfully demonstrate the use of the antigen formulation for the inhibition of tumor cell growth in vivo (column 20), and Hoefer *et al.* and Arteaga *et al.* successfully demonstrate the inhibition of tumor cell growth and metastases in vivo using a composition comprising a TGFβ antagonist. Thus, with the knowledge that both compositions, individually, are useful as anti-tumor agents, it

would have been obvious to combine the two compositions because one would have a reasonable expectation of success that the combination of the two agents would achieve a greater anti-tumor response than either agent alone.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
July 18, 2003